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[Intervention Review]

Cuffed versus uncuffed endotracheal tubes for general anaesthesia in children aged eight years and under

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ABSTRACT

Background

Since the introduction of endotracheal intubation in paediatrics, uncuffed endotracheal tubes (ETTs) have been the standard of care for children under eight years old, based on the presumption that complications, particularly postoperative stridor, are higher with cuffed ETTs. The major disadvantages of uncuffed ETTs cited for this shift in procedure include the difficulty in achieving tidal volumes due to leakage around an uncuffed ETT. To seal the airway adequately, uncuffed tubes may need to be exchanged for another tube with a larger diameter, which sometimes requires several attempts before the appropriate size is found. Uncuffed tubes also allow waste anaesthetic gases to escape, contributing significantly to operating room contamination and rendering the anaesthetic procedure more expensive. Our review summarizes the available data, to provide a current perspective on the use of cuffed versus uncuffed endotracheal tubes in children of eight years old or less.

Objectives

To assess the risks and benefits of cuffed versus uncuffed endotracheal tubes during general anaesthesia in children up to eight years old.

Search methods

We searched CENTRAL, MEDLINE, Embase, CINAHL, LILACS and Google Scholar databases from their inception until March 2017. We also searched databases of ongoing trials, and checked references and citations. We imposed no restriction by language.

Selection criteria

We included randomized and quasi-randomized controlled trials in which the effects of using cuffed and uncuffed tubes were investigated in children up to eight years old undergoing general anaesthesia. We excluded studies conducted solely in newborn babies.

Data collection and analysis

We applied standard methodological procedures, as defined in the Methodological Expectations of Cochrane Intervention Reviews (MECIR).

Main results

We included three trials (2804 children), comparing cuffed with uncuffed ETTs. We rated the risks of bias in all three trials as high. Outcome data were limited. The largest trial was supported by Microcuff GmbH, who provided the cuffed tubes used. The other two trials were small, and should be interpreted with caution. Based on the GRADE approach, we rated the quality of evidence as low to very low.

Two trials comparing cuffed versus uncuffed ETTs found no difference between the groups for postextubation stridor (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.65 to 1.33; 2734 children; quality of evidence very low). However, those two trials demonstrated a statistically significantly lower rate of endotracheal tube exchange in the cuffed ETT group (RR 0.07, 95% CI 0.05 to 0.10; 2734 children; quality of evidence very low).

One trial with 70 participants found that costs per case were lower in the cuffed ETT group (mean difference (MD) EUR 19.0 lower; 95% CI 24.23 to 13.77 lower; quality of evidence low), since the higher cost of the cuffed tubes may be offset by the savings made with anaesthetic gases.

No clear evidence emerged to suggest any difference between cuffed and uncuffed tubes for outcomes such as the need to treat postextubation stridor with tracheal re-intubation (RR 1.85, 95% CI 0.17 to 19.76; 115 children; 2 trials; quality of evidence very low), epinephrine (RR 0.70, 95% CI 0.38 to 1.28; 115 children; 2 trials; quality of evidence very low) or corticosteroid (RR 0.87, 95% CI 0.51 to 1.49; 102 children; 1 trial; quality of evidence very low), or need for intensive care unit (ICU) admission to treat postextubation stridor (RR 2.77, 95% CI 0.30 to 25.78; 102 children; 1 trial; quality of evidence very low).

None of the trials included in this review evaluated the ability to deliver appropriate tidal volume.

Authors' conclusions

Implications for practice

We are unable to draw definitive conclusions about the comparative effects of cuffed or non-cuffed endotracheal tubes in children undergoing general anaesthesia. Our confidence is limited by risks of bias, imprecision and indirectness. The lower requirement for exchange of tubes with cuffed ETTs was very low-quality evidence, and the requirement for less medical gas used and consequent lower cost was low-quality evidence. In some cases, tracheal re-intubation is required to guarantee an open airway when adequate oxygenation is difficult after removal of the tube, for a variety of reasons including stridor, muscle weakness or obstruction. No data were available to permit evaluation of whether appropriate tidal volumes were delivered.

Implications for research

Large randomized controlled trials of high methodological quality should be conducted to help clarify the risks and benefits of cuffed ETTs for children. Such trials should investigate the capacity to deliver appropriate tidal volume. Future trials should also address cost effectiveness and respiratory complications. Such studies should correlate the age of the child with the duration of intubation, and with possible complications. Studies should also be conducted in newborn babies. Future research should be conducted to compare the effects of the different types or brands of cuffed tubes used worldwide. Finally, trials should be designed to perform more accurate assessments and to diagnose the complications encountered with cuffed compared to uncuffed ETTs.

PLAIN LANGUAGE SUMMARY

Cuffed versus uncuffed tubes in children aged eight years and under, having general anaesthetic

Review question

Most surgical procedures may require general anaesthesia (a medically-induced state of unconsciousness in which a person feels nothing). Tracheal tubes (a device that is inserted into the windpipe to maintain a person's airway) play a vital role in the surgery. A mechanical ventilator is often needed to keep the patient breathing during anaesthesia. This is a machine that helps a person to breathe in oxygen and to breathe out carbon dioxide. There are two types of tracheal tubes: one is cuffed, with a balloon at the end of the tube providing proper tracheal sealing and preventing the stomach contents from getting into the lungs. The other is uncuffed, with no balloon. This review focuses on the different effects of cuffed and uncuffed tubes on children of up to eight years old during general anaesthesia.

Background

Children have a smaller and more fragile airway than adults. Their larynx is funnel shaped with the narrowest portion occurring at the cricoid cartilage. There is a belief that the risks of windpipe and voice box injuries in children are higher with the use of cuffed tubes, although this assumption is not based on current evidence.

The disadvantages of using an uncuffed tube are an increase in air leakage around the tube, making it difficult to ensure that the child is breathing adequate amounts of oxygen. In addition, the measurement of tidal volume (the normal volume of air displaced between breathing in and out, whether or not by mechanical ventilation) is compromised. It seems reasonable to suppose that cuffed tubes would be more likely to fit the trachea at the first attempt, whereas uncuffed tubes may require more attempts.

Cuffed versus uncuffed endotracheal tubes for general anaesthesia in children aged eight years and under (Review)

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Study characteristics

This review includes trials involving 2804 children up to eight years old, undergoing general anaesthesia. The trials assessed two types of cuffed tubes: conventional and Microcuff™ tubes (the latter consisting of a different type of balloon with low pressure levels that is more suitable for children's windpipes).

The primary outcome was postextubation stridor. This is a potentially serious problem resulting from the narrowing of the airway and can be identified by a high-pitched noise following removal of the tube. Other factors assessed were the need to exchange the tube for another; to put the tube back in; to use drugs such as epinephrine (adrenaline) or corticosteroid (an anti-inflammatory); and to admit a child to an intensive care unit to treat stridor; the cost of medical gas per child; and the ability to deliver appropriate volumes of oxygen.

Key results

Two trials (involving 2734 children) measured postextubation stridor and found no difference between the groups. The need to exchange tubes for others was 93% lower in the cuffed ETT group. One trial involving 70 children showed that cuffed tubes reduced the amount of anaesthetic gases required, and consequently the cost involved.

Quality of evidence

The quality of evidence was low to very low, as there were problems with the study designs. Comparisons between cuffed and uncuffed tubes need to be interpreted with caution. Further studies are needed to evaluate the benefits and risks of the two types of tubes.

Conclusion and future research

Several gaps remain in the information available around this question. Large, well-conducted clinical trials should clarify factors such as the ability of these tubes to provide adequate amounts of oxygen, and the respiratory complications that occur with the wide use of cuffed tubes in children.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Cuffed vs uncuffed tubes for children up to eight years undergoing general anaesthesia

Cuffed vs uncuffed tubes for children up to eight years who underwent general anaesthesia

Patient or population: Children up to eight years undergoing general anaesthesia

Settings: Various European and North American paediatric anaesthesia centres conducting general anaesthesia with tracheal intubation

Intervention: Cuffed tubes

Control: Uncuffed tubes

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Cuffed tubes				
Postextubation stridor (defined as any inspiratory sound or persistent barking, or presence of sternal or intercostal retractions postextubation)	Study population		RR 0.93 (0.65 to 1.33)	2734 (2 studies)	⊕⊕⊕⊕ very low 1, 2, 3	-
	44 per 1000	40 per 1000 (28 to 58)				
	Moderate					
	38 per 1000	35 per 1000 (25 to 51)				
Need for ETT exchange (defined as more than one attempt to arrive at the final endotracheal tube size)	Study population		RR 0.07 (0.05 to 0.10)	2734 (2 studies)	⊕⊕⊕⊕ very low 1, 2, 4	-
	293 per 1000	21 per 1000 (15 to 29)				
	Moderate					
	268 per 1000	19 per 1000 (13 to 27)				
Need for tracheal re-intubation for post-operative stridor (defined as the need to re-intubate to assure oxygenation to deal with postextubation stridor)	Study population		RR 1.85 (0.17 to 19.76)	115 (2 studies)	⊕⊕⊕⊕ very low 1, 2, 3	-
	18 per 1000	33 per 1000 (3 to 353)				

	Moderate					
	10 per 1000	19 per 1000 (2 to 198)				
Need for epinephrine to treat stridor (defined as the need to use epinephrine to treat postextubation stridor)	Study population		RR 0.7 (0.38 to 1.28)	115 (2 studies)	⊕⊕⊕⊕ very low 1, 2, 3	-
	321 per 1000	225 per 1000 (109 to 402)				
	Moderate					
	367 per 1000	257 per 1000 (125 to 459)				
Need for intensive care unit (ICU) admission to treat post extubation stridor (as defined by the trial authors)	20 per 1000	57 per 1000 (6 to 526)	RR 2.77 (0.30 to 25.78)	102 (1 study)	⊕⊕⊕⊕ very low 5, 6	-
Cost of medical gas (described in the study by the hospital expenses for medical gases per participant in Euros)	The mean cost of medical gas in the control groups was 25 euros 7	The mean cost of medical gas in the intervention groups was 19 euros lower (24.23 to 13.77 lower)	-	70 (1 study)	⊕⊕⊕⊕ low 8	-
Need for corticosteroid to treat stridor (defined as the need to use corticosteroid to treat postextubation stridor)	224 per 1000	195 per 1000 (114 to 334)	RR 0.87 (0.51 to 1.49)	102 (1 study)	⊕⊕⊕⊕ very low 5, 6	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹One study was quasi-randomized and was an open trial. The other trial, although randomized, presented performance and detection bias. Final decision: we downgraded by two levels (very serious) for study limitation.

²Trials compared two different cuffed tubes. We downgraded by one level (serious) for indirectness.

³The confidence interval was wide and crossed the line of no effect, indicating clinically-meaningful differences with either tube type. Final decision: we downgraded by one level (serious) for imprecision.

4The cumulative sample size reached the optimal information size.

5This outcome comes from a single trial. Although it was a large study, performance bias was inevitable and detection bias was not clear. Also, the microcuff tubes was supplied by Microcuff GmbH. Final decision: we downgraded by two level (very serious) for trial limitations.

6A single trial assessed this outcome, providing a limited number of participants, which caused problems with the precision (wide confidence interval). We downgraded by one level (serious) for imprecision.

7The assumed risk (score) used was the mean.

8 One small study analysed this outcome. Performance bias was inevitable, selection and detection bias were not clear and also sample size calculation was not described. Final decision: we downgraded by two level (very serious) for trial limitation.

BACKGROUND

Description of the condition

During paediatric anaesthesia, general endotracheal intubation is commonly performed for airway management and positive pressure ventilation (Bhardwaj 2013). Traditionally, uncuffed endotracheal tubes (ETTs) are recommended for children up to eight years old (Mukhopadhyay 2016). This is based on the anatomical peculiarities of the airways of young children in whom the circumferential and non-distensible cricoid cartilage is the narrowest point of the airway (Taylor 2011; Veyckemans 1999). In addition, the rationale for using uncuffed ETTs in small children is based on the fact that the airway surfaces of their epiglottis and cricoid are lined with loose areolar connective tissue that is prone to the formation of oedema. Concern has been expressed that using a cuffed ETT could promote laryngeal and tracheal injury, as well as impairing tracheal mucosal blood flow and compressing the mucosa within the unyielding cricoid ring (Bhardwaj 2013; Brambrink 2002; James 2001). All of these complications are associated with a higher incidence of postextubation laryngeal oedema and tracheal stenosis (Deakers 1994).

Using an uncuffed ETT with appropriate leakage theoretically decreases the likelihood of these complications. The uncuffed ETTs of choice are therefore those large enough to seal the cricoid ring, enabling adequate positive pressure ventilation while still allowing air leakage at a pressure of 20 to 30 cm H₂O to avoid excessive pressure on the tracheal mucosa (Aker 2008; Engelhardt 2006; Taylor 2011). Finding an uncuffed ETT that meets the ideal criteria remains a challenge and may require additional or even multiple tube changes before the appropriate size is found (Dalal 2009; Khine 1997). It is common to have to make a choice between an uncuffed ETT with a tight seal (i.e. more than 30 cm H₂O) and one that offers greater leakage. The former often exerts undue pressure on the laryngeal structures, causing laryngeal injury (Sathyamoorthy 2013). Even when leakage is present, the pressure that is exerted on some parts of the cricoid mucosa may still be excessive. However, a larger air leak around the uncuffed ETT leads to unreliable monitoring of the ventilatory parameters, exhaled volumes and end-expiratory gases, which may be particularly important in major surgeries or in the case of high-risk patients (Weber 2009; Weiss 2004).

With larger airway leaks, despite the low risk of compression of the mucosa within the unyielding cricoid, modern anaesthesia machines may actually turn off some of their monitors of ventilatory parameters. Additionally, although modern ventilators are increasingly incorporating more sophisticated lung function measurements such as lung compliance and resistance, these measurements are not accurate in the presence of an airway leak (Ashtekar 2005; Engelhardt 2006; James 2001). Furthermore, airway leaks with uncuffed ETTs increase the depletion of anaesthetic gases, with economic implications. There is also a higher risk of aspiration, particularly in children undergoing emergency abdominal surgeries (Eschertzhuber 2010).

Support for the use of cuffed ETTs has been growing over the past 10 years. Some authors believe that, with the use of appropriately-designed cuffed ETTs, with cuff pressure control and the correct size of tube, the likelihood of a successful fitting at the first attempt is much higher than with uncuffed tubes (Aker 2008; Dorsey 2010; Taylor 2011; Veyckemans 1999; Weiss 2009). In recent studies

conducted using low-pressure and high-volume cuffed types of ETT, safety has been shown to be greater when the correctly-sized ETT is chosen and cuff inflation is measured to maintain a leak at a pressure of 20 to 30 cm H₂O (Deakers 1994; Taylor 2011; Weiss 2009).

Despite some evidence suggesting that the use of cuffed ETTs does not lead to more serious adverse events compared with the use of uncuffed ETTs, some anaesthesiologists remain reluctant to use cuffed tubes in small children (Allen 1972; Fine 2004; Flynn 2008; Strong 1977). Our review focuses on the benefits and possible disadvantages of cuffed and uncuffed endotracheal tubes.

Description of the intervention

During general anaesthesia, children can be intubated with either cuffed or uncuffed ETTs. The use of uncuffed ETTs is standard practice for children of up to eight years old (Dorsey 2010; Mukhopadhyay 2016). Recently improved manufacturing processes and materials have resulted in cuffed ETTs appropriate for children, prompting more practitioners to use them in this population. Modern high-volume cuffed ETTs have low pressure, with the distance from the vertex of the bend to the tip adapted to the child's anatomy (Dullenkopf 2004; Hunyady 2015; Kutter 2013). This avoids both endobronchial intubation and the cuff lying between the vocal cords (Dorsey 2010; Veyckemans 1999), which decreases the likelihood of laryngeal and tracheal injury or of impaired tracheal mucosal blood flow.

We focus on the benefits of cuffed ETTs, due to their superior ability to seal the airway and the purported lack of airway morbidity. Another factor evaluated was whether cuffed ETTs are more likely to fit at the first attempt than uncuffed tubes when used appropriately and when the cuff pressure is routinely measured (Flynn 2008; Khine 1997; Raman 2012; Weiss 2009).

How the intervention might work

Cuffed ETTs provide a seal below the larynx that may offer several advantages over uncuffed ETTs during general anaesthesia in children. These include reducing the risk of aspiration and contamination, and improving ventilation and end-tidal carbon dioxide monitoring. The need to exchange the tube is also reduced, with no increased risk of postextubation stridor compared with uncuffed ETTs (Calder 2012; Dorsey 2010; Fine 2004; Raman 2012).

Why it is important to do this review

Some authors have suggested that the use of cuffed tracheal tubes in children under eight years old would eliminate the disadvantages found with uncuffed tubes and should therefore be considered when selecting a tube for a child of that age (Dorsey 2010; Veyckemans 1999). Studies have highlighted the benefits of cuffed ETTs, and some authors believe that when comparing cuffed and uncuffed ETTs in young children cuffed ETTs are not associated with higher airway morbidity (Flynn 2008; Khine 1997; Raman 2012; Weiss 2009). No meta-analysis has yet been conducted on this topic. A review of the subject would improve quantification of the treatment outcomes by increasing the power and precision currently provided in studies in which there are conflicting results and opinions on the use of uncuffed versus cuffed ETTs. It is imperative when comparing uncuffed versus cuffed ETTs either to support the continued use of an existing paradigm or to sustain a shift to a new, emerging paradigm, with the results benefiting clinical practice either way (James 2001). Strong and

well-supported scientific evidence on this topic would therefore improve quality and safety in clinical practice, particularly given the continued growth of major high-risk procedures in small, critically-ill children in whom there is a greater need to maintain effective delivery of ventilation and inhalation anaesthetics.

OBJECTIVES

To assess the risks and benefits of cuffed versus uncuffed endotracheal tubes during general anaesthesia in children up to eight years old.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs), quasi-randomized controlled trials (the method of allocation is known but is not considered strictly random, e.g. date of birth, medical record number) and cluster-randomized trials conducted in children of eight years old or less, undergoing general anaesthesia.

We excluded studies that were solely conducted in newborn babies; however, specific subgroups from such studies are included in the analysis.

Types of participants

We included children ranging in age from newborn up to eight years old who had required tracheal intubation during general anaesthesia.

We chose eight years old as the cut-off point, due to the anatomical differences in a child's larynx and trachea up to that age. After the age of eight, most children have a laryngotracheal anatomy that is similar to that of teenagers and adults in its size, dimensions and orientation. The likelihood of any laryngotracheal issues in children over eight years of age is similar to that of adults.

The planned methodology was to include studies with a mix of children of various ages, as long as most of the children in the study were below the age of eight and required tracheal intubation during general anaesthesia.

Types of interventions

The aim of the review was to compare cuffed and uncuffed endotracheal tubes (ETTs) used for endotracheal intubation during general anaesthesia.

Intervention group: cuffed endotracheal tubes

Control group: uncuffed endotracheal tubes

Types of outcome measures

Primary outcomes

1. Postextubation stridor (defined as any inspiratory sound or a persistent barking, or presence of sternal or intercostal retractions postextubation)

Secondary outcomes

1. Need for ETT exchange (defined as more than one attempt to arrive at the final endotracheal tube size)
2. Need for tracheal re-intubation for postoperative stridor (defined as the need to re-intubate to assure oxygenation to deal with postextubation stridor)
3. Need for epinephrine treatment for stridor (defined as the need to use epinephrine to treat postextubation stridor)
4. Need for corticosteroid treatment for stridor (defined as the need to use corticosteroid to treat postextubation stridor)
5. Need for intensive care unit (ICU) admission to treat postextubation stridor (as defined by trial authors)
6. Ability to deliver appropriate tidal volume (as defined by trial authors)
7. Cost of medical gas (described in the study by the hospital expenses for medical gases per patient in euros)

Search methods for identification of studies

Electronic searches

We searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL; 2017 issue 12) ([Appendix 1](#)), MEDLINE via PubMed (January 1966 to March 2017) ([Appendix 2](#)), Embase via Elsevier (January 1980 to March 2017) ([Appendix 3](#)), CINAHL via EBSCOhost (January 1982 to March 2017) ([Appendix 4](#)), LILACS (January 1985 to March 2017) ([Appendix 5](#)), SCIELO (January 1996 to March 2017) ([Appendix 6](#)) and Google Scholar (January 2004 to March 2017) ([Appendix 7](#)).

We conducted the search using combined free-text words and controlled vocabulary/MeSH terms with no limitation by the period of research. We used the MEDLINE search terms for each database.

We tried to identify all relevant studies regardless of language or publication status (published, unpublished).

Searching other resources

We handsearched reference lists in review articles, RCTs, quasi-randomized controlled trials, cluster-randomized trials and editorials to identify additional studies. We also searched the databases of ongoing trials (January 1990 to March 2017), including those registered at:

- www.controlled-trials.com/;
- clinicaltrials.gov/.

Data collection and analysis

Selection of studies

Two review authors (FAO and RGACA) independently evaluated the abstracts of all the publications obtained using the search strategies referred to in the [Electronic searches](#) to select potentially relevant studies. We entered the reasons for excluding any study into the Review Manager 5 file ([RevMan 5](#)). When we deemed studies eligible, we obtained the full articles to enable us to assess their relevance based on our predefined inclusion criteria. Throughout the evaluation, we discussed any disagreements and, if necessary, consulted a third review author (AL).

Data extraction and management

We used a data collection form to record data extracted from the articles (see [Appendix 8](#)). In the case of eligible studies, two review authors (FAO and RGACA) independently extracted the data from the original publications onto the standardized form, discussing any disagreements about the studies during the evaluation and, if necessary, consulting a third review author (AL). We entered the data into the [RevMan 5](#) file and cross-checked them for accuracy.

Assessment of risk of bias in included studies

Two review authors (FAO and RGACA) applied the Cochrane tool for assessing risks of bias in randomized trials to evaluate the selected RCTs ([Higgins 2004](#); [Higgins 2011](#)). We assessed each trial according to the following methodological quality domains: generation of the allocation sequence, allocation concealment, blinding of the investigators and the participants, blinding of the outcome assessors, incomplete outcome data, selective reporting and other potential sources of bias. We then classified the risk of bias for each item as low, high or unclear.

We considered the risk of bias to be low in a trial if we rated all the domains as adequate. Conversely, we considered the risk of bias to be high in a trial if we rated two or more domains as inadequate or unclear (if the data available to assess the method used are insufficient, this is likely to introduce confounding). Performance bias was inevitable in this type of intervention, since anaesthesiologists cannot be totally blinded to which type of tube is being used, as they need to visualize the tube passing through the vocal cords to ensure tracheal intubation. We conducted sensitivity analyses to determine whether excluding studies with a high risk of bias affected the results of the meta-analysis.

Assessment of the quality domains :

1. Sequence generation (checking for possible selection bias)

We evaluated each included study for whether the method used to generate the allocation sequence was reported in sufficient detail to allow us to make an assessment about whether it would produce comparable groups.

We assessed the methods as:

- low risk of bias (any truly random process, e.g. table of random numbers; computer-generated random-number list);
- high risk of bias (odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

2. Allocation concealment (checking for possible selection bias)

For each included study, we described the method used to conceal allocation to interventions prior to assignment and judged whether the intervention allocation could have been foreseen in advance of or during recruitment, or changed after it had been assigned.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomization; consecutively-numbered, sealed opaque envelopes);

- high risk of bias (open random allocation; unsealed or non-opaque envelopes);

- unclear risk of bias.

3. Blinding (checking for possible performance bias)

3.1 Blinding of participants and personnel

For each included study, we described the methods used, if any, to blind study participants and personnel from being aware of which intervention a participant received. We considered studies to have a low risk of bias if they were blinded or if we deemed that the lack of blinding would be unlikely to affect the results. We assessed blinding separately for different outcomes and classes of outcome.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

3.2 Blinding of outcome assessment (checking for possible detection bias)

For each included study, we described the methods used, if any, to blind outcome assessors from becoming aware of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcome.

We evaluated the methods used to assess the outcome of blinding as having a:

- low, high or unclear risk of bias.

4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

For each included study and for each outcome or class of outcome, we analysed the completeness of data, including attrition and exclusions from the analysis. We described whether attrition and exclusions were reported, as well as the numbers included in the analysis at each stage (compared with the total number randomized). We also described the reasons for attrition or exclusion when reported, and whether missing data were balanced across groups or were related to outcomes. Where the trial authors reported or could provide sufficient information, we re-included the data missing from the analyses performed.

We assessed the methods as:

- low risk of bias;
- high risk of bias (numbers or reasons for missing data are unbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization);

- unclear risk of bias.

5. Selective reporting bias

For each included study, we described how the possibility of selective outcome reporting bias was investigated and what was found.

We assessed the methods as having:

- low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);

- high risk of bias (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes was not prespecified; outcomes of interest are reported incompletely, hence cannot be used; the study fails to include results of a key outcome that would have been expected to have been reported);

- unclear risk of bias.

6. Other bias (checking for bias due to problems not covered by items 1 to 5 above)

For each included study, we described any important concerns about other possible sources of bias.

We made an assessment about the presence of other problems that could result in a risk of bias:

- low risk of other biases;
- high risk of other biases;
- unclear whether there is risk of other biases.

7. Overall risk of bias

We made explicit judgements about whether studies were subject to a high risk of bias in accordance with the criteria provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to domains 1 to 6 above, we assessed the magnitude and direction of the bias to establish whether this was likely to have had an impact on the findings. We investigated the impact of the level of bias by conducting a sensitivity analysis (see below, section on [Sensitivity analysis](#)). Two review authors (FAO and RGACA) created plots of risk of bias using the Review Manager 5 (RevMan 5) software.

We present 'Risk of bias in included studies' tables (Figure 2 and Figure 3). The section [Characteristics of included studies](#) provides detailed information about the included studies.

Measures of treatment effect

Dichotomous data

We defined dichotomous outcomes as the presence or absence of an effect (for example, postextubation stridor). We present results as summary risk ratios (RR) with a 95% confidence interval (CI). We planned to calculate the numbers needed to treat for an additional beneficial outcome (NNTB) or for an additional harmful outcome (NNTH), as appropriate.

Continuous data

One of our outcomes was a measure of continuous data (cost of medical gas), and was reported using medians with range, from which we calculated the mean and standard deviation (SD) using an agreed formula (Hozo 2005). We planned to use the mean difference (MD) for outcomes measured in the same way in the trials, or the standardized mean difference (SMD) for those measured by different methods. If this was not reported, we obtained the SMD from the confidence intervals or P values that were reported for differences in mean values between two groups (Higgins 2011). However, these approaches were not necessary, because currently only one trial reports the cost of medical gas.

Unit of analysis issues

Cluster-randomized trials

If we included any cluster-randomized trials in the review, we conducted sensitivity analyses to investigate the robustness of their conclusions. To avoid unit-of-analysis errors, we conducted the analysis at the same level as the allocation, using a summary measurement from each cluster. The effective sample size of a single intervention group was its original sample size divided by the 'design effect'. Although we planned to include cluster-randomized trials, we have not so far found any eligible trials with this kind of design.

Cross-over trials

The nature of the intervention (endotracheal intubation) means that it did not seem feasible (or ethical) that a study would be designed where a participant would change their group after a washout period (impossible in this situation). A study where a person would serve as their own control, such as in a cross-over design, seemed unlikely for the same reasons. We therefore did not expect and did not find any cross-over trials with our primary outcomes of interest.

Studies with multiple treatment groups

Our study deals with rates (primarily binary yes/no variables), so we needed information on the rate for each binary outcome to perform our meta-analysis. In a study presenting multiple outcomes, we planned to use the measure of interest (such as postextubation stridor) in the meta-analysis. Furthermore, if a study did not report this rate but it appeared that the authors may have the information, we would then try to contact the authors to obtain the necessary information.

After application of the eligibility criteria, there were no studies with multiple treatment groups.

Dealing with missing data

In the case of missing data we conducted where possible an intention-to-treat (ITT) analysis for all outcomes. That is, we attempted to include all participants randomized to each group in the analyses, and all participants were analysed in the group in which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomized minus any participants whose outcomes were known to be missing (Borenstein 2008). For studies with more than the conventionally acceptable 20% rate of attrition, we contacted the first author of the trial for additional data on those participants lost to follow-up. We performed 'best case versus worst case' sensitivity analysis.

Assessment of heterogeneity

We assessed clinical heterogeneity of the included studies according to their clinical and methodological diversity ('Risk of bias' assessments). We planned to address clinical heterogeneity using subgroup and sensitivity analyses (Higgins 2011). If we detected substantial heterogeneity, we considered whether a pooled result would be meaningful and, if it was, we would have used a random-effects model, presenting the results as the estimated average treatment effect with a 95% CI, as the 95% prediction interval for the underlying treatment effect.

We assessed heterogeneity in each meta-analysis using the I^2 and χ^2 statistics. We regarded heterogeneity as substantial if the I^2 statistic exceeded 30%, or if the P value was less than 0.10 in the χ^2 test for heterogeneity; or if there was clearly substantial inconsistency between trials in the direction or magnitude of effects, as judged by visual inspection.

As we did not find substantial heterogeneity, we presented the results as fixed-effect analyses. We assessed clinical heterogeneity between the different types of cuffed tubes (microcuffed and conventional) using subgroup and sensitivity analyses (Higgins 2011).

Assessment of reporting biases

We had planned to assess publication bias and other small-study effects using a funnel plot, and to test for funnel plot asymmetry using variance-stabilizing regression methods (Harbord 2006; Rücker 2008); however, because this approach requires at least 10 studies to be implemented and our review includes only three, we were unable to apply these tests.

Data synthesis

We assessed heterogeneity among studies through visual inspection of the forest plots and the use of the I^2 statistic. If we identified significant heterogeneity (I^2 statistic > 30%), we used a random-effects model; otherwise, we incorporated a fixed-effect model (Higgins 2003). We performed the meta-analysis using the Review Manager 5 software (RevMan 5).

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroup analyses as described in the protocol (De Orange 2015), but this was not possible due to insufficient data:

- Age group:
 - 0 to 28 days
 - 29 days to 24 months
 - > 24 months
- Duration of endotracheal intubation
 - < 40 minutes
 - > 40 minutes
- Gestational age:
 - Preterms
 - Appropriate for gestational age

We used the primary outcomes in the subgroup analysis. Rates of:

- Postextubation stridor
- ETT exchange
- Tracheal re-intubation for postoperative stridor

Sensitivity analysis

We planned to carry out a sensitivity analysis to explore the effects of fixed-effect or random-effects models for each outcome variable with statistical heterogeneity, but this was not necessary due to the low heterogeneity ($I^2 < 30\%$) among the studies.

We carried out sensitivity analysis to explore the effect of trial quality (RCT versus quasi-RCT) for the primary outcome (postextubation stridor). We planned to conduct a sensitivity analysis to determine whether or not excluding studies with a high risk of bias affected the results of the meta-analysis. Finally, we carried out a sensitivity analysis to explore the effects of different kinds of cuffed tubes (microcuff or conventional) on the primary outcomes.

'Summary of findings' table and GRADE

We used the GRADE approach (GRADEpro), to assess the quality of the body of evidence in our review that is associated with specific outcomes (Guyatt 2008):

1. Postextubation stridor
2. Need for ETT exchange
3. Need for tracheal re-intubation for postoperative stridor
4. Need for epinephrine treatment for stridor
5. Need for corticosteroid treatment for stridor
6. Need for ICU admission to treat postextubation stridor
7. Cost of medical gas (per child in euros)

We constructed a 'Summary of findings' table, using the GRADE software (GRADEpro). We created the 'Summary of findings' table to provide outcome-specific information that includes an assessment of the overall quality of evidence. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers the risk of bias within the study (methodological quality), the directness of the evidence, the heterogeneity of the data, the precision of effect estimates and the risk of publication bias. Based on these items we downgraded the evidence from 'high quality' by one level for serious infringements, or by two levels for very serious infringements.

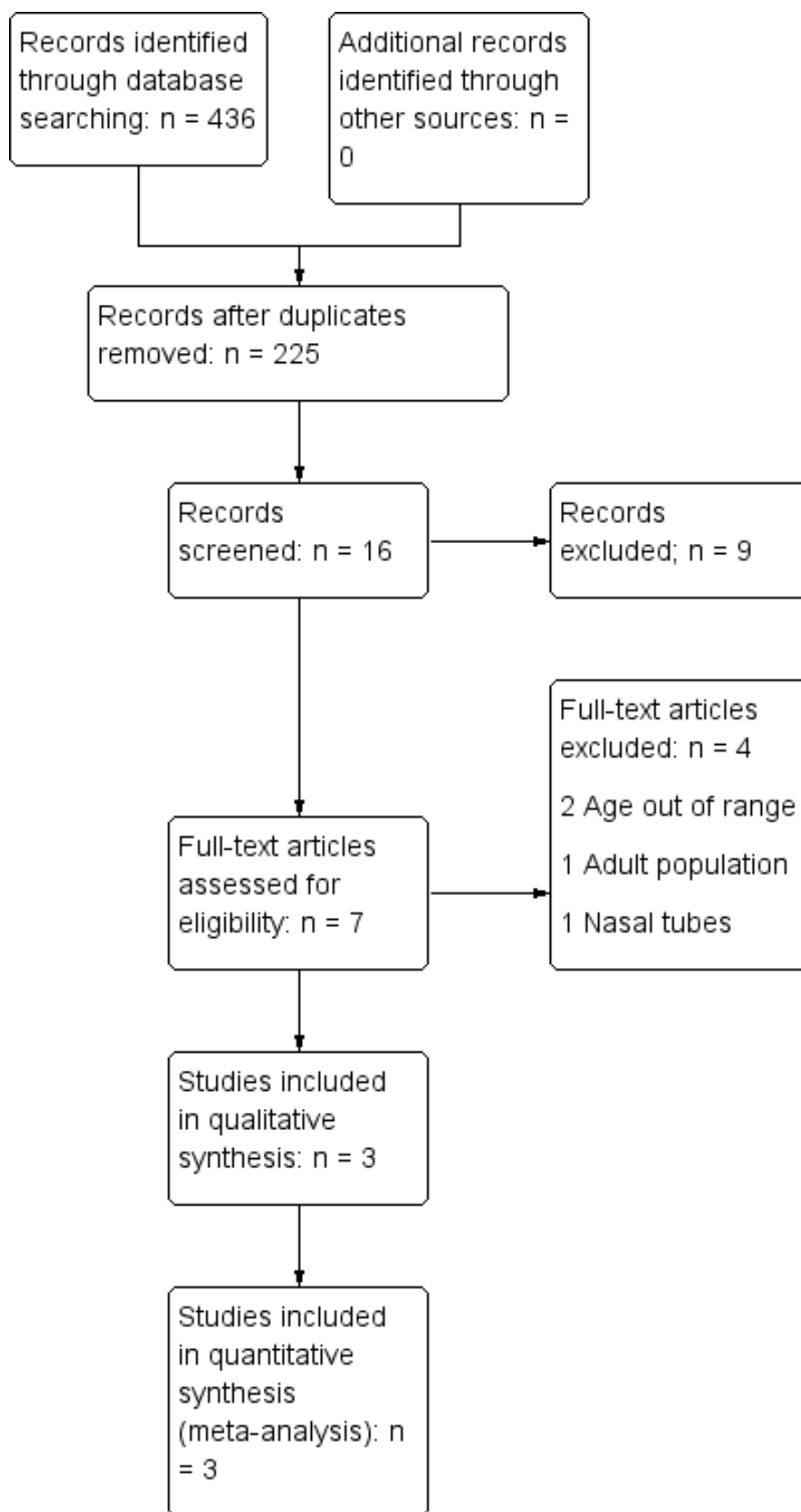
RESULTS

Description of studies

Results of the search

See Figure 1.

Figure 1. Study flow diagram



We retrieved 436 studies from the databases. After removing duplicates, we analysed 225 reports, and excluded 218 of them. We read the full reports of the remaining seven randomized controlled trials. We excluded four of the seven RCTs for not meeting the eligibility criteria (see section on [Characteristics of excluded studies](#)). As of March 2017, we have identified no currently ongoing clinical trials.

We include three RCTs in the review. We present a full description of these studies in the section [Characteristics of included studies](#).

Included studies

We include three trials in the review, involving 2804 children in whom cuffed endotracheal intubation (intervention) was compared with uncuffed tubes during general anaesthesia in children from birth to five years old ([Eschertzhuber 2010](#); [Weiss 2009](#)), and from birth to eight years old ([Khine 1997](#)). The three trials were conducted in the USA ([Khine 1997](#)), and Switzerland ([Eschertzhuber 2010](#); [Weiss 2009](#)). One study was commercially funded ([Weiss 2009](#)).

In one study ([Khine 1997](#)), the mean age was higher (3.1 years) than that of the other studies ([Eschertzhuber 2010](#); [Weiss 2009](#)) (1.7 and 1.8 years respectively). In the largest study ([Weiss 2009](#)), there were more boys than girls, and the mean weight was 11.3 ± 4.6 kg. The highest mean weight described was 14.7 ± 7.5 kg ([Khine 1997](#)), since this study included older children. Gender differences were not reported in the studies.

The reported surgical procedures consisted of ophthalmological, otolaryngological, abdominal, urological and orthopaedic procedures or head and neck surgery ([Eschertzhuber 2010](#); [Khine](#)

[1997](#); [Weiss 2009](#)). Although data on intubation time were not available for all three studies, the duration of the longest procedure was 103 ± 76.3 minutes ([Weiss 2009](#)).

In [Khine 1997](#), the intervention was carried out with three different types of cuffed tubes. Both [Eschertzhuber 2010](#) and [Weiss 2009](#) used only Microcuff™ tubes in the intervention group.

The cuff pressure was limited to 20 to 25 cm H₂O in the intervention group in all three trials. The control groups in the trials used conventional uncuffed tubes in accordance with the age of each child.

Excluded studies

We excluded four trials for the following reasons: one analysed a different intubation approach of cuffed tubes (nasal versus oral) ([De Armendi 2015](#)). The second trial included an adult population ([Byhahn 2000](#)). Finally, [Engelhardt 2006](#) and [Mukhopadhyay 2016](#) included children aged up to 13 and 12 years respectively, which were outside the eligible age range for this review.

Ongoing studies

We identified no ongoing studies.

Studies awaiting classification

There are no studies awaiting classification.

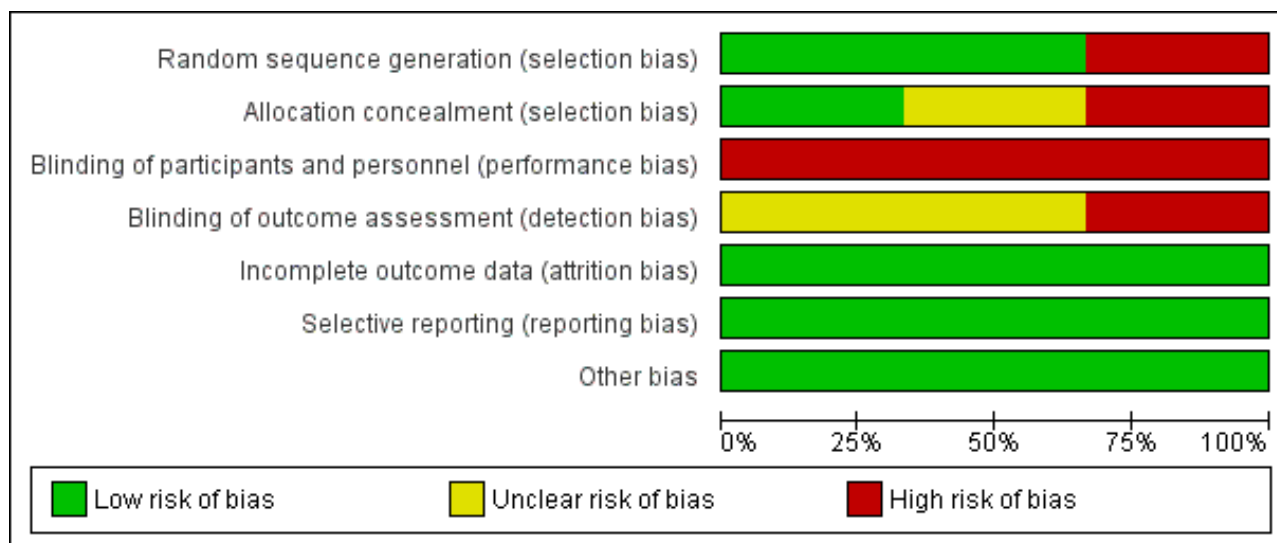
Risk of bias in included studies

For a summary of the risks of bias for the included studies, see [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Eschertzhuber 2010	+	?	-	?	+	+	+
Khine 1997	-	-	-	-	+	+	+
Weiss 2009	+	+	-	?	+	+	+

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Sequence generation

We considered that the randomization process was adequate (computer-generated) in two trials ([Eschertzhuber 2010](#); [Weiss 2009](#)). We rated both trials at low risk of bias and both compared cuffed tubes versus uncuffed tubes. We judged the risk of selection bias for [Khine 1997](#) as high, because the method used for randomization was sequential medical records.

Allocation concealment

For [Weiss 2009](#), we rated the risk of allocation concealment bias as low because the procedure was adequately described. [Eschertzhuber 2010](#) failed to describe the allocation concealment procedure and was therefore rated at unclear risk of bias. Finally, we judged the risk of bias in [Khine 1997](#) to be high, since it was a quasi-randomized trial.

Blinding

Blinding of participants and personnel

As the participants were anaesthetized for the intervention (cuffed tubes) they were always blinded. However, it was not possible to blind the personnel who applied the intervention. We therefore considered the risk of bias to be high in all three trials.

Blinding of outcome assessment

Two of the three trials did not describe who was responsible for blinding of outcome assessment, and so were considered to be at unclear risk of bias ([Eschertzhuber 2010](#); [Weiss 2009](#)). We rated [Khine 1997](#) at high risk of bias, since the study stated that outcome assessment was not blinded.

Incomplete outcome data

All three included studies were classified as being at low risk of attrition bias, as they did not report any loss or changes between the groups.

Selective reporting

We found no reporting bias, since all prestated outcomes were fully assessed by the included studies.

Other potential sources of bias

There was a clear conflict of interest in [Weiss 2009](#), since it had been supported by the Microcuff™ company that provided the cuffed tubes for the trial.

Effects of interventions

See: [Summary of findings for the main comparison Cuffed vs uncuffed tubes for children up to eight years undergoing general anaesthesia](#)

See [Summary of findings for the main comparison](#)

Primary outcome

1. Postextubation stridor (defined as any inspiratory sound or a persistent barking, or presence of sternal or intercostal retractions postextubation)

Two trials (2734 children; [Khine 1997](#); [Weiss 2009](#)) reported on this outcome. There was no difference between the groups (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.65 to 1.33; $P = 0.70$; $I^2 = 0\%$; [Analysis 1.1](#)). We downgraded the finding by one level from high to moderate for imprecision (the confidence interval was wide). We then downgraded from moderate to very low quality evidence for very serious bias (two levels) in study limitation and indirectness (one level) for two different types of cuffed tubes used.

We carried out a sensitivity analysis of an RCT versus a quasi-randomized design, and found no difference in the results. The randomized trial ([Weiss 2009](#)) produced a RR of 0.95, 95% CI 0.65 to 1.39; $P = 0.78$, while the quasi-randomized trial ([Khine 1997](#)) had an RR of 0.81, 95% CI 0.28 to 2.37; $P = 0.70$; ([Analysis 1.1](#)). Heterogeneity was absent, with an $I^2 = 0\%$.

The same analysis demonstrated no difference between the use of Microcuff™ and conventional tracheal tubes in the primary outcome.

Secondary outcomes

1. Need for endotracheal tube exchange (ETT) (defined as more than one attempt to arrive at the final endotracheal tube size)

Two trials (2734 children) (Khine 1997; Weiss 2009) measured this outcome. They found a difference between the groups (RR 0.07, 95% CI 0.05 to 0.10; $P = 0.68$; $I^2 = 0\%$), confirming a 93% lower rate of endotracheal tubes exchange in the intervention group (Analysis 1.2). However, this result was from very low-quality evidence, due to study limitations and was downgraded by two levels (one study was quasi-randomized and the second trial showed performance and detection bias). Indirectness was also found (downgraded one level).

2. Need for tracheal re-intubation for postoperative stridor (defined as the need to re-intubate to assure oxygenation to deal with postextubation stridor)

Two trials tested the need for tracheal re-intubation for postoperative stridor (115 children) (Khine 1997; Weiss 2009). The results showed no evidence of a significant difference (RR 1.85; 95% CI 0.17 to 19.76; $P = 0.61$) (Analysis 1.3). This result, however, was derived from studies of very low quality, with problems in study limitations, indirectness and imprecision.

3. Need for epinephrine or corticosteroid treatment for stridor (defined as the need to use epinephrine or corticosteroids to treat postextubation stridor)

3.1 Epinephrine

Two trials looked at the use of epinephrine (115 children) (Khine 1997; Weiss 2009). There was no evidence of a difference between the groups in the need for epinephrine for the treatment of this complication (RR 0.70, 95% CI 0.38 to 1.28; $P = 0.24$; heterogeneity was absent, with an I^2 of 0%) (Analysis 1.4). Because of study limitation (reduced by two levels), indirectness (decreased by one level), imprecision (decreased by two levels) we rated the evidence as very-low quality.

3.2 Corticosteroid

Corticosteroid use was reported in one trial (102 children) (Weiss 2009). This study found no evidence of difference between the groups (RR 0.87, 95% CI 0.51 to 1.49; $P = 0.62$) (see Table 1). This result, however, is derived from a trial in which we rate the quality of evidence as very low. As shown in Summary of findings for the main comparison, the risk of bias was high (downgraded two levels because of performance bias and a lack of clarity about the blinding of outcome assessors), problems with imprecision (downgraded two levels because of the width of the confidence interval) and indirectness (downgraded one level).

4. Need for intensive care unit (ICU) admission to treat postextubation stridor (as defined by trial authors)

One trial reported this outcome (102 children) (Weiss 2009), with no evidence of any significant difference (RR 2.77, 95% CI 0.3 to 25.78; $P = 0.37$) (see Table 1). This result, however, is from a study rated very low-quality evidence, with serious study limitations, indirectness

and imprecision (downgraded two levels because of the width of the confidence interval).

5. Ability to deliver appropriate tidal volume (as defined by trial authors)

None of the trials reported this outcome.

6. Cost of medical gas (defined as the costs for medical gases per child in euros)

Only one trial with 70 participants reported this outcome (Eschertzhuber 2010). This analysis showed that the mean cost of medical gas in the intervention group was EUR 19/patient less than in the control group (mean difference (MD) 19.0 lower; 95% CI 24.23 to 13.77 lower; $P < 0.001$); (see Table 1). This result was from a study that we rated as low-quality evidence. We downgraded from high to low (two levels) because of study limitations such as a performance bias and because concealment of the allocation and blinding of the outcome assessors were unclear.

DISCUSSION

Summary of main results

Despite the possible disadvantages of using cuffed endotracheal tubes (ETTs), which include the purported increased risk of postextubation stridor, their use in paediatric anaesthesia has been increasing. Clinical practice anecdotally supports this transition, as practitioners experience the disadvantages of using uncuffed ETTs, including the need to exchange ETTs until an appropriate fit is achieved, and the waste of anaesthetic gases escaping into the operating room. Moreover, the inability to monitor ventilatory parameters with uncuffed ETTs when using modern anaesthesia machine ventilators, which are more sensitive to these leaks, limits a practitioner's ability to effectively care for their smallest and sickest patients, and places these children at risk. Cuffed ETTs therefore appear to improve the anaesthetic care of patients without apparently increasing the risks of intubation, as was previously believed.

We found three trials (Eschertzhuber 2010; Khine 1997; Weiss 2009), involving 2804 children, in which cuffed ETTs were compared with uncuffed ETTs in children under eight years old undergoing general anaesthesia.

The results of this meta-analysis showed no evidence of any statistically significant difference in the development of postextubation stridor in the children who received cuffed ETTs compared to those receiving uncuffed ETTs. However, it has to be emphasized that these findings are derived from studies in which the quality of evidence is classified as very low, due to the limitations of the studies included in the review (bias risk) (Khine 1997; Weiss 2009). Furthermore, there were problems with imprecision. It must be noted that the different types of cuffed ETTs used in the studies may have contributed to the lack of difference between the groups. For example, Khine 1997 used the Mallinckrodt™ Lo-Pro, oral RAE or Sheridan low-pressure cuffed ETT, whereas Eschertzhuber 2010 and Weiss 2009 used the Microcuff™, creating problems with indirectness. Taken together, these factors contributed to a decrease in the quality of the evidence. The need to exchange ETTs was significantly lower in the cuffed ETT group, with a 93% lower requirement for ETT tube exchanges compared to the uncuffed group. Due to the limitations

previously described, the quality of evidence of the studies on which this finding is based is very low.

We found no significant differences in the need for tracheal re-intubation or for epinephrine to treat postextubation stridor. Again, the quality of this evidence was classified as very low. The secondary outcomes concerning the need for corticosteroids and admission to an ICU, analysed in only one study, showed no difference between the groups (Weiss 2009). This finding was also derived from a study in which the quality of the evidence was considered low, mainly due to the study being commercially funded.

Finally, when the cost of anaesthetic gases was compared between groups, costs were significantly lower in the cuffed group. However, this finding came from a single study in which the risk of bias was classified as high (performance bias was present and there were unclear levels of selection and detection bias) (Eschertzhuber 2010).

Overall, the low quality of the evidence makes it impossible for this review to reach any conclusion about the benefits and disadvantages of cuffed versus uncuffed ETTs.

Overall completeness and applicability of evidence

Two trials included in this review provided evidence addressing the primary outcome, and three of the secondary outcomes (ETT exchange, tracheal re-intubation and epinephrine treatment) (Khine 1997; Weiss 2009). However, of three additional secondary outcomes, corticosteroid treatment and ICU admission were assessed only by Weiss 2009, while the cost of medical gas was evaluated only by Eschertzhuber 2010. The ability to deliver an appropriate tidal volume was not assessed, as we found no acceptable studies measuring this parameter. The present findings are therefore limited because of the range and quality of the available evidence.

The characteristics of the clinical trials may also limit the external applicability of their results, for the following reasons. Firstly, the three studies (Eschertzhuber 2010; Khine 1997; Weiss 2009) were conducted either in the USA or in Europe; we found no trials from Latin America or Asia, thus restricting the study population. Secondly, in two trials (Khine 1997; Weiss 2009), different methods were used to select the size of the tube in accordance with the child's age. Thirdly, the studies measured the pressure in the cuff and limited it to a narrow range of 20 to 25 cm H₂O to permit adequate perfusion of the tracheal mucosa and avoid potential ischaemia, whereas in clinical practice the pressure range may be wider, either by choice or due to a lack of measurement capabilities. Finally, the criteria used to extubate participants were not categorized, which may constitute a confounding factor, as the depth of anaesthesia at the time of extubation may play a role in the onset of complications, particularly postextubation stridor.

Another issue compromising applicability lies in the fact that two of the three studies (Khine 1997; Weiss 2009) used different cuffed ETTs for the primary outcome and for most of the secondary outcomes. Khine 1997 used the Mallinckrodt™ Lo-Pro, oral RAE or Sheridan low-pressure cuffed tubes. In contrast, the children in Eschertzhuber 2010 and Weiss 2009 were intubated only with a Microcuff™ ETT. An example of the importance of this confounding factor is that the Mallinckrodt™ Lo-Pro is a low-profile spherical cuff

with much greater potential to inflate to high pressures, whereas the Microcuff™ ETT is a low-profile cylindrical cuff that is considered a higher-volume low-pressure cuff. The consistency of these results is therefore impaired, although this was somewhat mitigated by the use of a cuff pressure limit for the various ETTs in both studies. Whether the differences between these various ETTs are significant enough to have altered the outcomes remains to be determined.

An important point to emphasize is that specific ETTs (particularly the Microcuff™ ETT as used in Eschertzhuber 2010 and Weiss 2009) are not routinely used worldwide, and this may affect applicability. Indeed, the Microcuff™ ETT is not available in most low- and middle-income countries, with the most important reason being the high cost of these devices.

Furthermore, although the initial plan was to analyse the data in subgroups according to the children's age, the duration of surgery and gestational age, the data available were insufficient to enable us to conduct such an analysis. This lack of data may have had an effect on the feasibility of extrapolating the results and also considerably limits a more accurate analysis of the potential benefits and disadvantages of these interventions.

Quality of the evidence

Evidence from this review comparing cuffed with uncuffed ETTs (Khine 1997; Weiss 2009) comes from trials in which we rated the risk of bias as high; it should therefore be interpreted with caution. According to GRADEpro, the overall quality of evidence for the primary and critical outcome reported (postextubation stridor) was very low. It was downgraded two levels for risks of bias. One study included in the review was quasi-randomized (Khine 1997), and demonstrated several biases (selection, performance and detection) (See Summary of findings table 1; Figure 2; Figure 3). Although the other study was randomized (Weiss 2009), we judged the risks of performance and outcome assessment biases as unclear. Weiss 2009 was supported by Microcuff GmbH, who provided cuffed tubes, which may represent an important risk of bias. The other two trials should be interpreted with caution, because they were small. As the studies compare different types of cuffed ETTs, we downgraded them by one level for indirectness. Imprecision was responsible for a downgrading by one level (for the width of the confidence interval, showing clinical differences between the two type of cuffed tube) (Peters 2006; Weiss 2009, see Summary of findings table 1).

We downgraded the result for the need to exchange ETT, classifying the quality of the evidence as very low. Although there was no problem with imprecision for this outcome (as the width of the confidence interval was acceptable and the optimal data size was obtained), this outcome came from the same limited studies as mentioned above (Khine 1997; Weiss 2009). Following the GRADEpro approach, we rated this as a serious study limitation (downgraded by two levels) and indirectness (downgraded by one level).

For the other secondary outcomes for the treatment of postextubation stridor, such as: tracheal re-intubation, epinephrine or corticosteroid use and ICU admission, we graded the quality of the evidence as very low. As reported (Khine 1997; Weiss 2009), there were several limitations to these studies (high risk of bias; Figure 2; Figure 3), resulting in a downgrade by one level for indirectness (two different types of cuffed tubes were used) and

by two levels for imprecision, (width of the confidence interval). Using [GRADEpro](#), all of these factors contributed to the low quality of evidence for these outcomes.

This review is based on only three trials, with one trial contributing 83% of the weight of the meta-analysis. The results therefore reflect the findings of this large trial ([Weiss 2009](#)). Furthermore, that study was commercially funded, significantly impairing the quality of the evidence and raising questions about the accuracy of the results.

Only one study ([Eschertzhuber 2010](#)) evaluated the cost of medical gas. We rated the level of evidence as low, downgrading it by two levels because of study limitations (performance bias, and the fact that allocation concealment and the blinding of the outcome assessors were unclear) (Summary of findings table 1).

Finally, whether cuffed ETTs have any impact on delivery of appropriate tidal volume remains unclear, given that none of the studies addressed this outcome.

Some important limitations need to be emphasized: firstly, few trials dealing with this topic have been published (we found only three RCTs that we could include). In addition, there were several flaws in these studies that affected the quality of evidence ([GRADEpro](#)); it is therefore impossible to support or reject any change in current practice.

Potential biases in the review process

Biases in the review process were minimized by following the methodology established in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). The evidence of this review came from a detailed search process that included published and unpublished papers and imposed no restrictions by language. It is possible that we failed to identify potentially eligible studies published in journals that are not indexed or difficult to access using this search strategy. Furthermore, there may be a time-lag bias (studies that have been completed but not yet published).

There may have been biases in the analyses conducted for this review. When comparing cuffed versus uncuffed tubes, one trial ([Eschertzhuber 2010](#)) reported continuous variables such as medians and ranges for the cost in euros of the medical gas used in the procedures. In this review, we have used a statistical method ([Hozo 2005](#)) to estimate means and standard deviations, and this could have caused an over- or underestimation of the overall effect.

In addition, in the protocol for this review ([De Orange 2015](#)) we planned an analysis of subgroups, as well as a comparison between groups for the ability to deliver appropriate tidal volume. These analyses were not feasible because of insufficient data in the included studies. The protocol also proposed a sensitivity analysis for the trials in which the risk of bias was classified as high; however, it proved impossible to implement this approach as risk of bias was high in all three included studies. These missing data could represent a potential source of bias.

The changes made to the original protocol for this review ([De Orange 2015](#)) resulted in no substantial alterations to the conclusions of the full review (see [Differences between protocol and review](#)). For example, we initially decided to assess the need for epinephrine or corticosteroid to treat postextubation stridor; however, we found that these two medical treatments had to be

analysed separately. In our opinion, this revised approach provides greater clarity.

Agreements and disagreements with other studies or reviews

A single previous systematic review ([Shi 2015](#)) assesses current evidence for postextubation morbidity and the tracheal tube exchange rate of cuffed compared to uncuffed tubes in children. That review included two RCTs and two cohort studies, unlike our review which includes only RCTs or quasi-RCTs. [Shi 2015](#) was further limited, since it failed to assess the quality of the body of evidence in the RCTs. Secondly, there were no sensitivity analyses conducted on the different types of RCT (quasi-randomized versus randomized trials). In accordance with the results, [Shi 2015](#) concluded that cuffed ETTs reduce the need to exchange ETTs and do not increase the risk of postextubation stridor compared to uncuffed ETTs. However, the results of their meta-analysis are unreliable, since they did not perform a strict and careful examination of the studies included in their review or of their potential for bias, imprecision, inconsistencies and other limitations. Unlike our review, [Shi 2015](#) did not examine the cost of medical gas.

One randomized trial ([Engelhardt 2006](#)) showed that the traditional formula used to determine the size of uncuffed ETTs is unreliable, possibly leading to gross over- or underestimation of size and increasing the need to exchange the ETT. Our meta-analysis corroborated this finding, despite the disparities in age range, as that trial included children aged from 5 to 13 years old (median 10 years).

A second trial ([De Armendi 2015](#)) compared cuffed and uncuffed nasal ETTs of different sizes and brands in children aged two to 10 years (mean 4.7 years), and showed significantly higher levels of problematic tube positioning with nasal cuffed ETTs. However, the investigators did not evaluate the development of any complications, and it is therefore impossible to compare the results of that study with our review.

AUTHORS' CONCLUSIONS

Implications for practice

The quality of the evidence showing no difference between cuffed and uncuffed ETTs for postextubation stridor in children aged up to eight years undergoing general anaesthesia is very low. Furthermore, the quality of the evidence indicating no difference in the need to re-intubate, in the need for drugs such as epinephrine or corticosteroid, to admit a child to an intensive care unit to treat stridor, or in the ability to deliver appropriate volumes of oxygen was also very low ([GRADEpro](#)).

The quality of evidence showing an increase in the need to exchange the ETT in the uncuffed group compared to the cuffed group was very low ([GRADEpro](#)). We found single positive finding in the cost of medical gas, ([Eschertzhuber 2010](#)) revealing lower costs in the cuffed group, (quality of evidence rated low).

Implications for research

Further studies on this subject are required to consolidate the evidence base and to clarify the questions that have arisen. Large, multicentre RCTs of high methodological quality are required to meet these goals. Potential inquiries to pursue include:

1. Comparing cuffed versus uncuffed ETTs for their ability to monitor and provide adequate tidal volumes, as none of the studies included in this review addressed this outcome;
2. Evaluating the severity of respiratory complications related to endotracheal intubation, such as the need for epinephrine, corticosteroids or admission to an ICU (the two latter outcomes were described in only one study);
3. Correlating the age of the child and the duration of the procedure with possible complications related to endotracheal intubation;
4. Assessing the long-term complications of intubation in early life, such as stenosis and tracheomalacia;
5. Conducting specific studies in neonates, as this highly vulnerable age group is poorly represented in studies, and the risks and benefits remain unclear;
6. Determining and assessing more accurate tests for a diagnosis of laryngeal and tracheal injuries, other than postextubation stridor, which reflects a severe and advanced finding;
7. Comparing several brands of cuffed ETT to each other, identifying an evidence base for the use of such devices and determining better cuff and ETT designs;
8. Continuing to evaluate the cost involved in the choice of ETTs for intubation.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Eschertzhuber 2010

Methods	Randomized controlled multicentre trial conducted in 2010 (published in May 2010). Participants undergoing a general anaesthesia were randomly divided into 2 groups. Conventional uncuffed tube group or Cuffed endotracheal tubes group
Participants	<p>Total number of participants: 70</p> <p>Inclusion criteria: after written parental consent, children aged from birth (> 3 kg) up to 5 years aged had undergone elective surgery with general inhalational anaesthesia with sevoflurane, regional anaesthesia and tracheal intubation were consecutively included into the study</p> <p>Exclusion criteria: patients with known or suspected airway anomalies or difficult intubation, risk for aspiration, patients undergoing airway surgery and patients in whom age-corresponding tube size had been found to be inappropriate during previous anaesthetics</p> <p>Location of the study: Children's Hospital of Zurich, Switzerland and Medical University Innsbruck, Austria</p> <p>Intervention group (n = 35)</p> <p>Participant's age (years): 1.64 (0.01 – 4.78)</p> <p>Participant's weight (kg): 12 (3.4 – 20.0)</p> <p>Duration of investigation (mins): 56 (34 – 138)</p> <p>Inspiratory sevoflurane concentration (Vol %): 2.5 (1.2 – 3.7)</p> <p>Control group (n = 35)</p> <p>Participant's age (years): 1.75 (0.05 – 4.8)</p> <p>Participant's weight (kg) 9.8 (3.6 – 19.1)</p> <p>Duration of investigation (mins): 57 (18 – 177)</p> <p>Inspiratory sevoflurane concentration (Vol %): 2.5 (1.5 – 3.2)</p>
Interventions	<p>Experimental group: received uncuffed Mallinckrodt (Covicien, Athlone, Ireland) or uncuffed Sheridan (Respiratory Care, Temecula, CA) tracheal tubes</p> <p>Control group: received a Microcuff PET (Microcuff GmbH, Weinheim, Germany)</p> <p>There were no dropouts</p>
Outcomes	<p>The primary outcome was consumption and costs for sevoflurane and medical gases. The amount of liquid sevoflurane and the amount of medical gases used were measured using a formula:</p> <p>Calculation of volume of liquid sevoflurane used per hour:</p> $A = C \times FGF \times 60/20$ <p>(A = amount of liquid volatile used (ml/h); C = concentration of volatile agent (%); FGF = fresh gas flow (l/min); 60 = conversion factor for minutes to provide hourly consumption; 20 = conversion factor for approximation of vapour to liquid volume)</p>

Eschertzhuber 2010 (Continued)

Calculation of volume of medical gases used:

$$V = \text{FGF} \times D$$

V= volume of medical gases used (l); FGF = fresh gas flow (l/min)(separate for oxygen, nitrous oxide and air); D= duration (mins)

The costs for sevoflurane and medical gases, potential savings per minute using a cuffed ETT and the duration of the procedure needed to compensate the higher costs of a cuffed ETT were calculated

Notes	There were no funding source and no competing interests reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized by a computerized list into cuffed ETT or uncuffed ETT groups in 2 medical centres
Allocation concealment (selection bias)	Unclear risk	Children undergoing elective surgery with general inhalational anaesthesia
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind the personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There were no descriptions of blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no descriptions of attrition or exclusions from the analysis. In this study, 70 children aged from 0.01 to 4.8 years were studied. 34 children (16 uncuffed ETTs/18 cuffed ETTs) were studied in Innsbruck and 36 were studied in Zurich (19 uncuffed ETTs/17 cuffed ETTs)
Selective reporting (reporting bias)	Low risk	It was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported
Other bias	Low risk	There was no other bias.

Khine 1997

Methods	Quasi-randomized controlled trial conducted in 1997 (published in May 1997) The study used medical records numbers to proceed to randomization. Patients that were undergoing general anaesthesia were randomly divided into 2 groups Conventional uncuffed tube group or cuffed endotracheal tubes group
Participants	Total number of participants = 488 Inclusion criteria: Full-term newborns and children up to 8 years old who required general anaesthesia and tracheal intubation Exclusion criteria: children with a history or physical evidence of intrinsic or extrinsic airway obstruction or severe pulmonary disease or those who required nasotracheal intubation were excluded from the study Location of the study: duPont Hospital for Children, Wilmington, USA Intervention group (n = 251)

Cuffed versus uncuffed endotracheal tubes for general anaesthesia in children aged eight years and under (Review)

Khine 1997 (Continued)

Participant's age (years): 3.3 (\pm 2.4)

Participant's weight (kg): 15.1 (\pm 7.4)

Duration of investigation (mins): 55

Control group (n = 237)

Participant's age (years): 2.9 (\pm 2.2)

Participant's weight (kg) 14.3 (\pm 7.7)

Duration of investigation (mins): 60

There were no differences between the groups for type of procedure

Interventions	<p>Children with odd medical records numbers were assigned to the uncuffed tube group (n = 237) and used a Mallinckrodt lo-po, oral RAE, or Sheridan low-pressure cuffed tube.</p> <p>Those with even numbers were assigned to the uncuffed tube group (n = 251), and received a conventional uncuffed tube.</p> <p>The tracheal intubations were assigned randomly to receive either a cuffed endotracheal tube sized by a new formula (size(mm internal diameter) = (age/4) + 3), or an uncuffed tube sized by the modified Cole's formula (size(mm internal diameter) = (age/4) + 4)</p> <p>Cuff pressure was limited to 25 mmHg</p>
Outcomes	<p>The outcomes evaluated were the number of intubations required to achieve an appropriately-sized tube, the need to use more than 2 L/min fresh gas flow, the concentration of nitrous oxide in the operating room, and the incidence of croup</p>
Notes	<p>There were no funding source and no competing interests reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Children with odd medical record numbers were assigned to the cuffed tube group, and those with even numbers were assigned to the uncuffed tube group
Allocation concealment (selection bias)	High risk	Characterized as an open random allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	This study was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no description of attrition or exclusions from the analysis. There were 251 children in the cuffed group and 237 in the uncuffed group, with demographic characteristic comparable in both groups
Selective reporting (reporting bias)	Low risk	It was clear that all prespecified outcomes and all expected outcomes of interest to the review have been reported
Other bias	Low risk	There was no other bias.

Weiss 2009

Methods	The study was conducted in 2009. It was planned, and organized as a prospective, randomized, controlled multicentre trial by the Department of Anaesthesia, University Children's Hospital Zurich, Switzerland (accepted for publication in September 2009)
Participants	<p>Total number of participants = 2246</p> <p>Patients aged from birth to < 5 yrs in 24 European paediatric anaesthesia centres, requiring general anaesthesia with tracheal intubation</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> · Children aged from birth (weighing > 3 kg) to < 5 yrs · Children requiring orotracheal or nasotracheal intubation with a Magill shaped TT or preformed TT as a part of their anaesthetic care and planned controlled ventilation during the surgical/interventional/diagnostic procedure · Tracheal intubation performed using direct laryngoscopy · Extubation after the procedure in the operating theatre · Procedure performed in the supine position · Patients for elective and emergency surgery, interventions, or both if there was no risk of regurgitation or pulmonary aspiration · ASA physical status I and II · Written parental consent <p>Exclusion criteria:</p> <ul style="list-style-type: none"> · No parental written consent obtained · Known airway anomalies (airway stenosis, including Down's syndrome) · Known or suspected difficult intubation · Known need for abnormal tube size · Children at risk for regurgitation · Surgery of the larynx and/or of the trachea, neck, and/or upper oesophagus · Pulmonary diseases (concurrent pneumonia or bronchial infection, asthma requiring inhalation medication, pulmonary malformations) · ASA physical status > II · Fiberoptic intubation or alternative intubation technique · Planned postoperative ventilation in the ICU · Weight and/or height percentiles < 3% or > 97% <p>2406 completed data forms were returned from the study centres. 160 data forms (106 in the cuffed group/54 in the uncuffed group) had to be excluded because the age group or the TT size with regard to age group was not correctly selected. Finally, 2246 children from 24 study centres were investigated (1119/1127 cuffed/uncuffed tubes). 5 children (1 in the cuffed group/4 in the uncuffed group) remained intubated after operation and were not included in the assessment of postintubation morbidity</p> <p>Intervention group (n = 1197)</p>

Weiss 2009 (Continued)

Age of participants (yr) (mean (range)): 1.94 (0–4.99)

Weight of patients (kg) [mean (SD)]: 11.4 (\pm 4.7)

Gender (female/male): 33.1%/66.9%

ASA (I/II): 66.2%/33.8%

Duration of investigation (mins): 55

Control group (n = 1049)

Age of participants (yr) (mean (range)): 1.85 (0 – 4.98)

Weight of participants (kg) (mean (SD)): 11.2 (\pm 4.6)

Gender (female/male): 35.0%/65.0%

ASA (I/II): 33.4%/66.6%

There was no differences between the groups for the type of procedure

Interventions	Participants were prospectively randomized into a cuffed TT group, n = 1197, (Microcuff PET) and an uncuffed TT group, n = 1049, (Mallinckrodt, Portex, Rüschw, Sheridan) Cuff pressure was limited to 20 mmHg
Outcomes	Endpoints were incidence of postextubation stridor and the number of TT exchanges to find an appropriate-sized tube. For cuffed TTs, minimal cuff pressure required to seal the airway was noted; maximal cuff pressure was limited to 20 cm H ₂ O with a pressure release valve
Notes	The study was supported by Microcuff GmbH, Weinheim, Germany, by providing the cuffed tracheal tubes, cuff pressure manometers, and release valves for no charge. Also supported by the Swiss Society for Anaesthesia and Resuscitation (SGAR) by a study grant.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study was planned and organized as a prospective, randomized, controlled multicentre trial
Allocation concealment (selection bias)	Low risk	Study sites were provided with sealed, opaque, consecutively-numbered envelopes that contained the randomization code. The envelopes were opened immediately before induction of anaesthesia
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study sites were provided with sealed, opaque, consecutively-numbered envelopes that contained the randomization code. Blinding of participants was carried out by the anaesthesia, but because of the nature of the intervention it was not possible to blind the anaesthesiologist, and also there was no description of blinding personnel in this study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was no description of the blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no attrition bias

Weiss 2009 (Continued)

Selective reporting (reporting bias)	Low risk	It was clear that all prespecified outcomes and all expected outcomes of interest to the review have been reported
Other bias	Low risk	There was no other bias.

Acronyms and abbreviations referred to in this table

A: amount of liquid volatile used (ml/h); ASA: American Society of Anesthesiologists; C: concentration of volatile agent (%); cm H₂O: centimetre of water; D: duration (min); ETT: endotracheal tubes; FGF: fresh gas flow (l/min); ICU: intensive care unit; Kg: kilogram; l/min: Litres per minute

Min: minute; ml/h: millilitre per hour; mmHg: millimetres of mercury; N: numbers of participants in study; PET: paediatric endotracheal tube; RAE: Ring, Adair and Elwyn (inventors of this type of cuffed tube); SD: standard deviation; SGAR: Swiss Society for Anaesthesia and Resuscitation; TT: tracheal tube; V: volume of medical gases used (l); yr: year

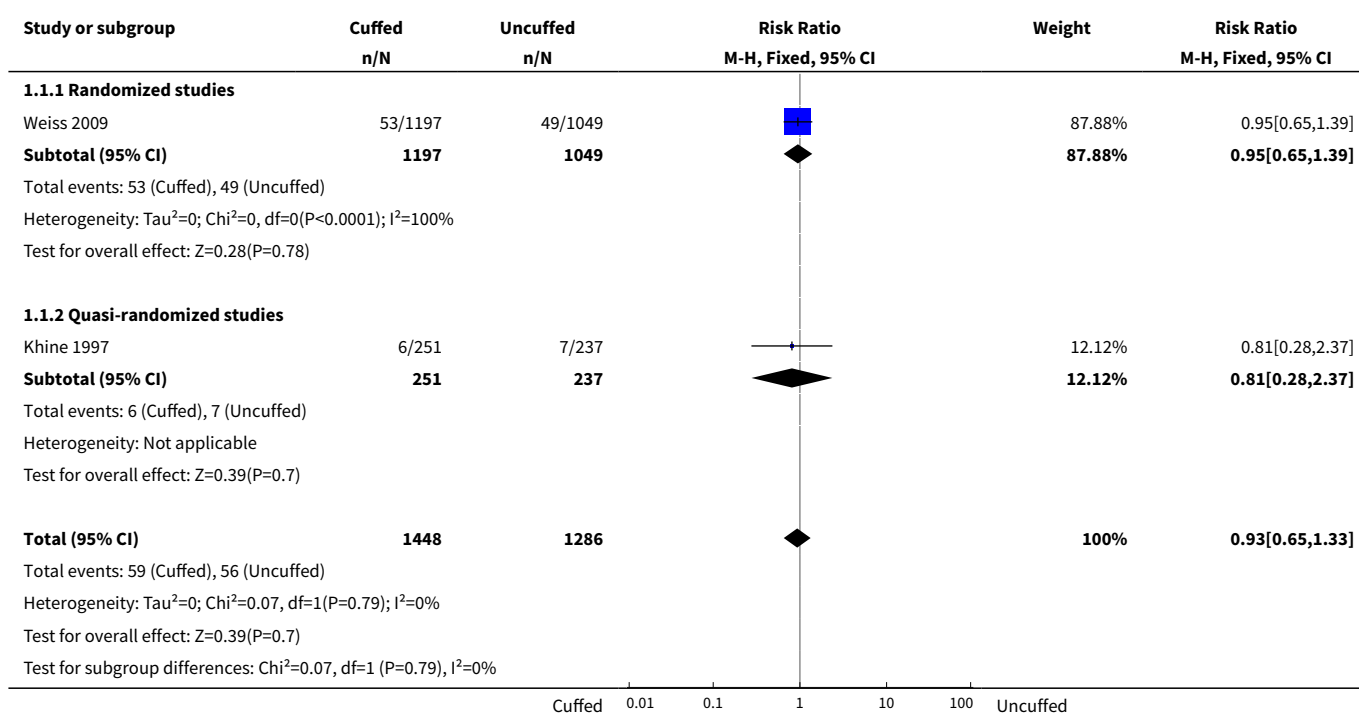
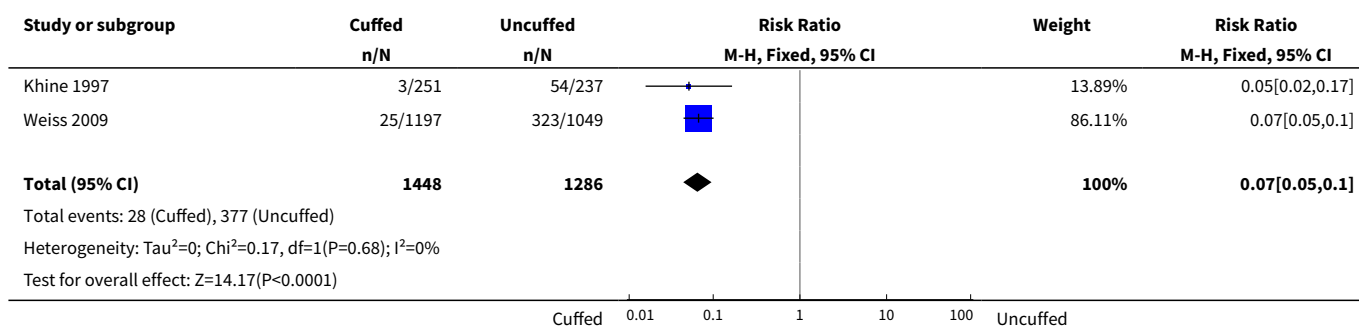
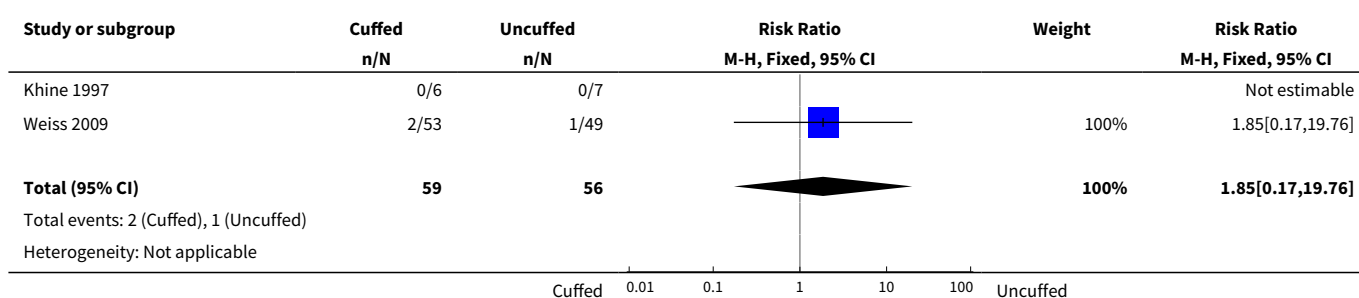
Characteristics of excluded studies [ordered by study ID]

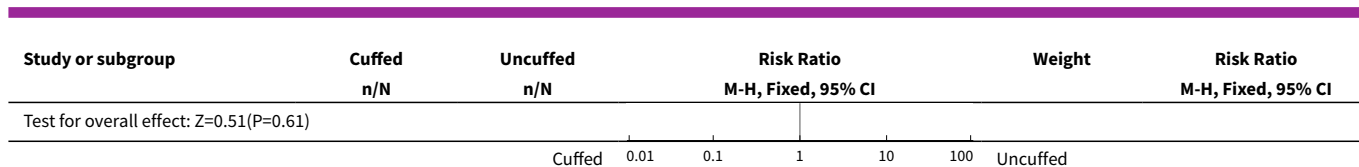
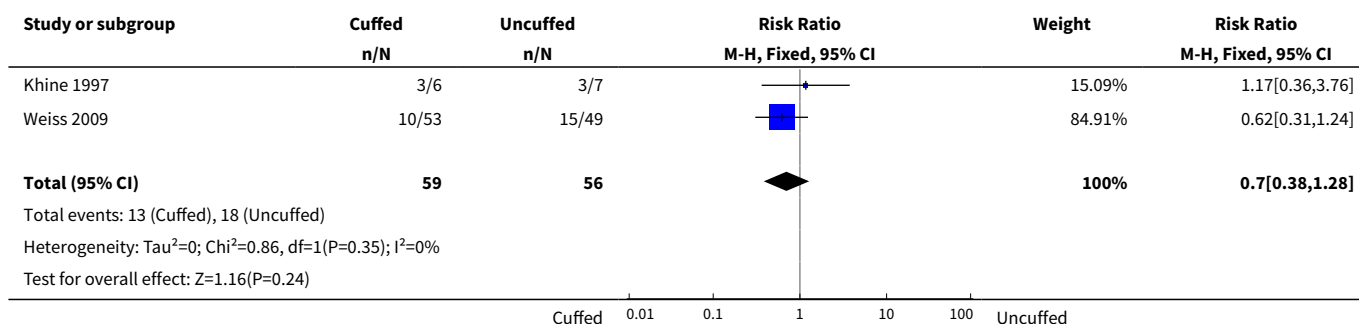
Study	Reason for exclusion
Byhahn 2000	The control group is an adult population. The age range of the paediatric group was not mentioned
De Armendi 2015	In this study the age group is eligible. The intervention was nasotracheal tubes and the control oral intubation approach
Engelhardt 2006	Age range out of the eligible range for this review
Mukhopadhyay 2016	Age of the study population above the eligible age range

DATA AND ANALYSES

Comparison 1. Cuffed versus uncuffed

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postextubation stridor	2	2734	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.65, 1.33]
1.1 Randomized studies	1	2246	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.65, 1.39]
1.2 Quasi-randomized studies	1	488	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.28, 2.37]
2 Need for ETT exchange	2	2734	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.05, 0.10]
3 Need for tracheal re-intubation for postoperative stridor	2	115	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [0.17, 19.76]
4 Need for epinephrine treatment for stridor	2	115	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.38, 1.28]

Analysis 1.1. Comparison 1 Cuffed versus uncuffed, Outcome 1 Postextubation stridor.**Analysis 1.2. Comparison 1 Cuffed versus uncuffed, Outcome 2 Need for ETT exchange.****Analysis 1.3. Comparison 1 Cuffed versus uncuffed, Outcome 3 Need for tracheal re-intubation for postoperative stridor.**

**Analysis 1.4. Comparison 1 Cuffed versus uncuffed, Outcome 4 Need for epinephrine treatment for stridor.****ADDITIONAL TABLES****Table 1. Trials comparing cuffed tubes versus uncuffed tubes**

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate	P value
Need for corticosteroid treatment for stridor	Weiss 2009	102	Risk Ratio (M-H, Fixed, 95% CI)	0.87 (0.51 to 1.49)	0.62
Need for ICU admission to treat postextubation stridor	Weiss 2009	102	Risk Ratio (M-H, Fixed, 95% CI)	2.77 (0.30 to 25.78)	0.37
Cost of medical gas	Eschertzhuber 2010	70	Mean Difference (IV, Fixed, 95% CI)	19.0 lower (24.23 to 13.77 lower)	< 0.001

ICU: Intensive care unit

APPENDICES**Appendix 1. CENTRAL search strategy**

ID Search Hits

#1 MeSH descriptor: [Pediatrics] explode all trees 655

#2 MeSH descriptor: [Child] explode all trees 213

#3 pediatry:ti,ab or pediatric*:ti,ab or child*:ti,ab or paediatric*:ti,ab or infant*:ti,ab or 'child':ti,ab or 'pediatrics':ti,ab 96663

#4 #1 or #2 or #3 96847

#5 (intubation:ti,ab or tube:ti,ab or tubes:ti,ab) and (intratrach*:ti,ab or endotrach*:ti,ab or trachea*:ti,ab or orotracheal:ti,ab) 5714

#6 cuff*:ti,ab or "HI-LO Evac":ti,ab or "KimVent Microcuff":ti,ab or "Profile Soft-Seal":ti,ab or Sacett:ti,ab or "Sheridan/HVT":ti,ab or TaperGuard:ti,ab 2479

#7 uncuff*:ti,ab or "non-cuffed":ti,ab or "non-cuff":ti,ab 52

#8 #5 and #6 399

#9 #5 and #7 36

#10 #4 and #8 and #9 12

Appendix 2. MEDLINE (Pubmed) search strategy

(Child[mh] OR pediatric*[tiab] OR child*[tiab] OR paediatric*[tiab] OR infant*[tiab]) AND (((intubation*[tiab] OR tubes[tiab] OR tube[tiab]) AND (intratracheal[tiab] OR endotracheal[tiab] OR trachea*[tiab] OR orotracheal[tiab])) AND (cuff*[tiab] OR "HI-LO Evac"[tiab] OR "KimVent Microcuff"[tiab] OR "Profile Soft-Seal"[tiab] OR Sacett[tiab] OR "Sheridan/HVT"[tiab] OR TaperGuard[tiab])) OR ("Intubation, Intratracheal"[mh] AND (cuff*[tiab] OR "HI-LO Evac"[tiab] OR "KimVent Microcuff"[tiab] OR "Profile Soft-Seal"[tiab] OR Sacett[tiab] OR "Sheridan/HVT"[tiab] OR TaperGuard[tiab]))) AND (((intubation*[tiab] OR tubes[tiab] OR tube[tiab]) AND (intratracheal[tiab] OR endotracheal[tiab] OR trachea*[tiab] OR orotracheal[tiab])) AND (uncuff*[tiab] OR non-cuffed[tiab] OR non-cuff[tiab])) OR ("Intubation, Intratracheal"[mh] AND (uncuff*[tiab] OR non-cuffed[tiab] OR non-cuff[tiab])))

Appendix 3. EMBASE (Elsevier) search strategy

pediatry:ti,ab OR pediatric*:ti,ab OR child*:ti,ab OR paediatric*:ti,ab OR infant*:ti,ab OR 'child'/exp OR 'child':ti,ab OR 'pediatrics'/exp OR 'pediatrics':ti,ab AND (intubation:ti,ab OR tube:ti,ab OR tubes:ti,ab AND (intratrach*:ti,ab OR endotrach*:ti,ab OR trachea*:ti,ab OR orotracheal:ti,ab) AND (cuff*:ti,ab OR 'hi-lo evac':ti,ab OR 'kimvent microcuff':ti,ab OR 'profile soft-seal':ti,ab OR sacett:ti,ab OR 'sheridan/hvt':ti,ab OR 'taperguard':ti,ab) OR ('endotracheal intubation'/exp OR 'endotracheal intubation' AND (cuff*:ti,ab OR 'hi-lo evac':ti,ab OR 'kimvent microcuff':ti,ab OR 'profile soft-seal':ti,ab OR sacett:ti,ab OR 'sheridan/hvt':ti,ab OR taperguard:ti,ab)) OR 'endotracheal tube cuff'/exp OR 'endotracheal tube cuff') AND (uncuff:ti,ab OR uncuffed:ti,ab OR 'non-cuffed':ti,ab OR 'non-cuff':ti,ab AND (intubation:ti,ab OR tube:ti,ab OR tubes:ti,ab) AND (intratrach*:ti,ab OR endotrach*:ti,ab OR trachea*:ti,ab OR orotracheal:ti,ab) OR ('endotracheal intubation'/exp OR 'endotracheal intubation' AND (uncuffed:ti,ab OR uncuff:ti,ab OR 'non-cuffed':ti,ab OR 'non-cuff':ti,ab))))

Appendix 4. CINAHL (EBSCOhost) search strategy

(pediatry OR pediatric* OR child* OR paediatric* OR infant*) AND ((intubation OR tube*) AND (intratrach* OR endotrach* OR trachea* OR orotracheal)) AND (uncuff* OR "non-cuffed" OR "non-cuff" OR "no cuff") AND ((intubation OR tube*) AND (intratrach* OR endotrach* OR trachea* OR orotracheal)) AND (cuff* OR "HI-LO Evac" OR "KimVent Microcuff" OR "Profile Soft-Seal" OR Sacett OR "Sheridan/HVT" OR TaperGuard)

Appendix 5. LILACS (BIREME) search strategy

tw:(((mh:'intubação intratraqueal' OR mh:'intubation, intratracheal' OR tw:'intubação intratraqueal' OR tw:'intubation, intratracheal') AND (tw:cuff* AND tw:uncuff*)) OR ((tw:intubat* OR tw:ett OR tw:tube* OR tw:tracheal*) AND (tw:cuff* AND tw:uncuff*)) AND ((pt:'ensaio clínico randomizado' OR tw:'randomized controlled trial' OR pt:'randomized controlled clinical trial') OR (mh: 'meta-analysis' OR mh:metanalise OR tw:'meta-analysis*' OR pt:'meta-analysis') OR (tw:'controlled clinical trial') OR (tw:randomized) OR (tw:placebo*) OR (tw:radomly*) OR (tw:trial*) OR (tw:groups))) AND (instance:"regional")

Appendix 6. SCIELO search strategy

(child* OR pediatric* OR paediatric* OR infant*) AND (uncuff* OR 'non-cuffed' OR 'non-cuff' OR 'without cuff' OR 'without cuffed') AND (cuff* OR 'hi-lo evac' OR 'kimvent microcuff' OR 'profile soft-seal' OR sacett OR 'sheridan/hvt' OR taperguard)

Appendix 7. Google Scholar searcg strategy

(child* OR pediatric* OR paediatric* OR infant*) AND (("Intubation, Intratracheal" OR "Intubation, Endotracheal") AND (cuff and (uncuffed OR "non cuff" OR "non cuffed" OR "without cuff"))) and (("meta-analysis" OR trial*))

Appendix 8. Data extraction form

Review title or ID

Study ID (*surname of first author and year first full report of study was published e.g. Smith 2001*)

Report IDs of other reports of this study (*e.g. duplicate publications, follow-up studies*)

Notes:

1. General information

Date form completed (*dd/mm/yyyy*)

Name/ID of person extracting data

Report title

(*title of paper/abstract/report that data are extracted from*)

Report ID

(*ID for this paper/abstract/report*)

Reference details

Report author contact details

Publication type

(*e.g. full report, abstract, letter*)

Study funding sources

(*including role of funders*)

Possible conflicts of interest

(*for study authors*)

Notes:

2. Study eligibility

Study characteristics	Eligibility criteria	Yes	No	Unclear	Location in text
	<i>(Insert eligibility criteria for each characteristic as defined in the protocol)</i>				<i>(pg & ¶/fig/table)</i>
Type of study	Randomized controlled trial				
	Controlled clinical trial				
	<i>(quasi-randomized trial)</i>				
Participants					
Children ranging in age from full-term neonates to 8 years of age who require tracheal intubation during general anaesthesia					
Types of intervention					
Cuffed versus uncuffed endotracheal tubes					
Types of outcome measures					
Primary outcomes					
1. Postextubation stridor(defined as any inspiratory sound or a persistent barking, or presence of sternal or intercostal retractions postextubation)					
Secondary outcomes					
1. Need for ETT exchange (defined as more than one attempt to arrive at the final endotracheal tube size)					
2. Need for tracheal re-intubation for postoperative stridor (defined as the need to re-intubate to assure oxygenation to deal with postextubation stridor)					
3. Need for epinephrine or corticosteroid treatment for stridor (defined as the need to use epinephrine or corticosteroids to treat postextubation stridor)					

(Continued)

4. Need for intensive care unit (ICU) admission to treat postextubation stridor (as defined by trial authors)

5. Ability to deliver appropriate tidal volume (as defined by trial authors)

6. Cost of medical gas (defined as the costs for medical gases per patient in euros)

INCLUDE

EXCLUDE

Reason for exclusion

Notes:

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3. Population and setting

	Description	Location in text
	<i>Include comparative information for each group (i.e. intervention and controls) if available</i>	<i>(pg & ¶/fig/table)</i>
Population description		
<i>(from which study participants are drawn)</i>		
Setting		
<i>(including location and social context)</i>		
Inclusion criteria		
Exclusion criteria		
Method/s of recruitment of participants		
Informed consent obtained	Yes No Unclear	
Notes:		

4. Methods

	Descriptions as stated in report/paper	Location in text
		<i>(pg & ¶/fig/table)</i>
Aim of study		
Unit of allocation		
<i>(by individuals, cluster/groups or body parts)</i>		
Start date		
End date		
Total study duration		
Ethical approval needed/obtained for study	Yes No Unclear	
Notes:		

5. 'Risk of bias' assessment

See Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Domain	Risk of bias			Support for judgement	Location in text (pg & ¶/fig/table)
	Low risk	High risk	Unclear		
Random sequence generation (selection bias)					
Allocation concealment (selection bias)					
Blinding of participants and personnel (performance bias)				Outcome group: all	
(if required)				Outcome group:	
Blinding of outcome assessment (detection bias)				Outcome group: all	
(if required)				Outcome group:	
Incomplete outcome data (attrition bias)					
Selective outcome reporting (reporting bias)					
Other bias					
Notes:					

6. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Total no. randomized (or total pop. at start of study for NRCTs)		
Baseline imbalances		
Withdrawals and exclusions		

(Continued)

(if not provided below by outcome)

Age

Sex

Race/ethnicity

Severity of illness

Co-morbidities

Other relevant sociodemographics

Subgroups measured

Subgroups reported

Notes:

7. Intervention groups

Copy and paste table for each intervention and comparison group

Intervention Group 1

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Group name		
No. randomized to group (specify whether no. people or clusters)		
Theoretical basis (include key references)		
Description (include sufficient detail for replication, e.g. content, dose, components)		
Duration of treatment period		
Timing (e.g. frequency, duration of each episode)		
Delivery (e.g. mechanism, medium, intensity, fidelity)		
Providers (e.g. no., profession, training, ethnicity etc. if relevant)		
Co-interventions		
Economic variables (i.e. intervention cost, changes in other costs as result of intervention)		

(Continued)

Resource requirements to replicate intervention

(e.g. staff numbers, cold chain, equipment)

Notes:

8. Outcomes

Copy and paste table for each outcome.

Outcome 1

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Outcome name		
Time points measured		
Time points reported		
Outcome definition (with diagnostic criteria if relevant)		
Person measuring/reporting		
Unit of measurement (if relevant)		
Imputation of missing data (e.g. assumptions made for ITT analysis)		
Assumed risk estimate (e.g. baseline or population risk noted in Background)		
Power		
Notes:		

9. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

Dichotomous outcome

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)

(Continued)

Comparison
Outcome
Subgroup
Time point
(specify whether from start or end of intervention)
Results
Intervention
Comparison

No. events

No. participants

No. events

No. participants

No. missing participants and reasons
No. participants moved from other group and reasons
Any other results reported
Unit of analysis *(by individuals, cluster/groups or body parts)*
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*
Reanalysis required? *(specify)*

Yes No Unclear

Reanalysis possible?

Yes No Unclear

Reanalysed results
Notes:
Continuous outcome

Description as stated in report/paper				Location in text (pg & ¶/ fig/table)		
Comparison						
Outcome						
Subgroup						
Time point (specify whether from start or end of intervention)						
Postintervention or change from baseline?						
Results	Intervention			Comparison		
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants
No. missing participants and reasons						
No. participants moved from other group and reasons						
Any other results reported						
Unit of analysis (individuals, cluster/groups or body parts)						
Statistical methods used and appropriateness of these methods (e.g. adjustment for correlation)						
Reanalysis required? (specify)			Yes No Unclear			
Reanalysis possible?			Yes No Unclear			
Reanalysed results						

(Continued)

Notes:

Other outcome

Description as stated in report/paper					Location in text (pg & ¶/fig/table)
Comparison					
Outcome					
Subgroup					
Results	Interven- tion result	SD (or other variance)	Control re- sult	SD (or oth- er variance)	
	Overall results		SE (or other variance)		
No. participants	Intervention		Control		
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					
Unit of analysis (by individuals, cluster/groups or body parts)					
Statistical methods used and appropriateness of these methods					
Reanalysis required? (specify)	Yes No Unclear				
Reanalysis possible?	Yes No Unclear				
Reanalysed results					
Notes:					

10. Applicability

Have important populations been excluded from the study? (consider disadvantaged populations, and possible differences in the intervention effect)	Yes No Unclear
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(Continued)

Is the intervention likely to be aimed at disadvantaged groups? (e.g. lower socioeconomic groups) Yes No Unclear

Does the study directly address the review question? Yes No Unclear

(any issues of partial or indirect applicability)

Notes:

11. Other information

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information (from whom, what and when)		
Notes:		

CONTRIBUTIONS OF AUTHORS

Flavia A De Orange (FO), Andrea Lemos (AL), , Paulo Sergio Gomes Nogueira Borges (PSGNB), Pete G Kovatsis (PK), Jose Figueroa (JF).

Conceiving the review: FAO, PSGNB, AL, AH and PK.

Co-ordinating the review: FAO.

Undertaking manual searches: FAO, RGA, PSGNB.

Screening search results: FAO, RGA, PSGNB.

Organizing retrieval of papers: FAO.

Screening retrieved papers against inclusion criteria: FAO, RGA, PSGNB.

Appraising quality of papers: FAO, RGA, PSGNB, AL.

Abstracting data from papers: FAO, RGA, PSGNB.

Writing to authors of papers for additional information: FAO, RGA, PSGNB.

Providing additional data about papers: FAO, RGA, PSGNB.

Obtaining and screening data on unpublished studies: FAO and PSGNB.

Data management for the review: FAO, RGA, AL.

Entering data into Review Manager 5 ([RevMan 5](#)): FAO.

RevMan statistical data: JF.

Other statistical analysis not using RevMan: JF.

Interpretation of data: JF.

Statistical inferences: JF, FAO, RGA, AL.

Writing the review: FAO, PK.

Securing funding for the review: FAO, PK.

Performing previous work that was the foundation of the present study: AL.

Guarantor for the review (one author): FAO.

Person responsible for reading and checking review before submission: FAO, PK.

DECLARATIONS OF INTEREST

Flavia A De Orange: none known.

Andrea Lemos: none known.

Cuffed versus uncuffed endotracheal tubes for general anaesthesia in children aged eight years and under (Review)

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Jose N Figueroa: none known.

Paulo Sergio Gomes Nogueira Borges: none known.

Pete G Kovatsis has been a Consultant for Verathon, Inc. since November 2017. He receives no direct compensation but the company reimburses his academic practice for his time and travel expenses

Rebeca GAC Andrade: none known.

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the pre-specified protocol ([De Orange 2015](#)):

1. A new author joined the team (Rebeca GAC Andrade), and another author left the review team (Amber M Hall), during the review process.
2. Initially the search was to be performed on MEDLINE and Embase, both via Ovid SP, by a Cochrane librarian. However, during the review process, the searches and their updates had to be conducted by the authors. Unfortunately, Ovid SP was not available in our region, so the searches were conducted on Embase from Elsevier and MEDLINE from PubMed. We believe that this change did not compromise the quality of the searches, since they were conducted with specific strategies by the main bases. They were submitted to the corrections and suggestions of the editorial group and after that we conducted a new update.
3. One outcome was revised from the protocol, which does not alter the meaning of the outcome nor its interpretation. For example, we needed to evaluate two medical treatments (epinephrine and corticosteroid) of stridor separately, to ensure precision and clarity of results.
4. Methods section: After the considerations by the editorial group, we added details to clarify some topics, such as: definition of a quasi-randomized study ([Types of studies](#)), explain how we assessed a study with an unclear risk of bias ([Assessment of risk of bias in included studies](#)), provide an example of a dichotomous outcome (Dichotomous data) and give the minimum number of studies necessary to perform the funnel plot ([Assessment of reporting biases](#)).
5. We standardized the percentage for significant heterogeneity to > 30%.
6. We used a statistical method by [Hozo 2005](#), to estimate means and standard deviations (from median values) from continuous data ([Eschertzhuber 2010](#)), for the outcome: cost of medical gas.
7. We state that the cost of medical gases was measured in euros.
8. We planned to assess the ability to deliver appropriate tidal volume as a secondary outcome. However, we were unable to carry it out, as none of the trials evaluated this aim directly.
9. We planned to carry out participant subgroup analyses (considering age group, duration of endotracheal intubation and gestational age), but there were too few trials and they did not provide sufficient data for these subgroups.
10. We planned to carry out sensitivity analyses to verify the impact on results by excluding studies at high risk of bias, but all the included trials were classified as high risk of bias, making it impossible to use this approach.

INDEX TERMS

Medical Subject Headings (MeSH)

*Equipment Design; Adrenal Cortex Hormones [therapeutic use]; Anesthesia, General [*instrumentation]; Bronchodilator Agents [therapeutic use]; Epinephrine [therapeutic use]; Intensive Care Units, Neonatal [statistics & numerical data]; Intubation, Intratracheal [adverse effects] [economics] [*instrumentation]; Randomized Controlled Trials as Topic; Respiratory Sounds [etiology]

MeSH check words

Child; Child, Preschool; Humans; Infant